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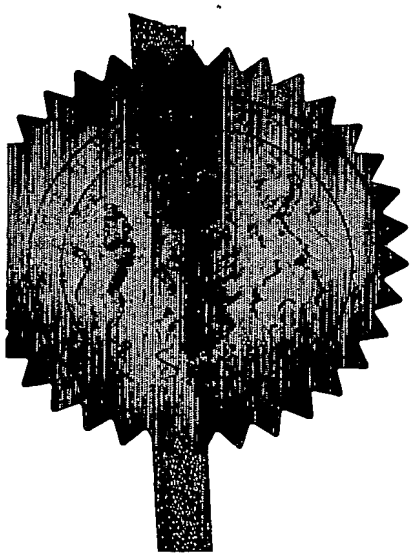

Signed Andrew Gerrard

Dated 29 October 2003

PCT/EP 03/12 01

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

1/77

THE PATENT OFFICE
B
31 OCT 2002
LONDON

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — ARG/DAB/P33136

2. Patent application number *(The Patent Office will fill in his part)* — 0225384.7

01NOV02 E760130-1 D01030
P01/7700 0.00-0225384.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)* 07358700 3

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* 07255500 6

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	21
Claim(s)	6
Abstract	1
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature _____ Date 30-Oct-02

A R Gladwin

12. Name and daytime telephone number of person to contact in the United Kingdom: A R Gladwin 01279 644934

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After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed tf it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
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c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
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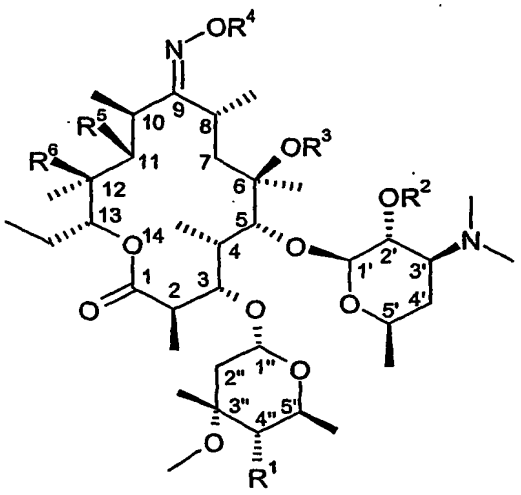
Compounds

The present invention relates to novel semi-synthetic macrolides having antibacterial activity. More particularly, this invention relates to novel oxime macrolide scaffolds substituted at the 4" position, to processes for their preparation, to compositions containing them and to their use in medicine.

Thus, the present invention provides compounds of general formula (I)



(I)

wherein

R^1 is $OC(O)(CH_2)_mXR^7$;

R^2 is hydrogen or a hydroxyl protecting group;

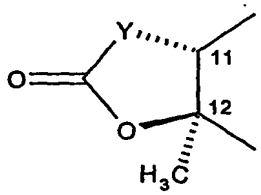
R^3 is hydrogen, C_{1-4}alkyl or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R^4 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl or a 5 or 6 membered heterocyclic group, wherein the alkyl, cycloalkyl, alkenyl and heterocyclic groups are optionally substituted by up to three substituents independently selected from optionally substituted 5 or 6 membered heterocyclic group, optionally substituted 5 or 6 membered heteroaryl, OR^8, $S(O)_nR^8$, NR^8R^9, $CONR^8R^9$, halogen and cyano;

R^5 is hydroxy, C_{3-6}alkenyloxy optionally substituted by 9 to 10 membered fused bicyclic heteroaryl or $O(CH_2)_pO(CH_2)_qR^{10}$,

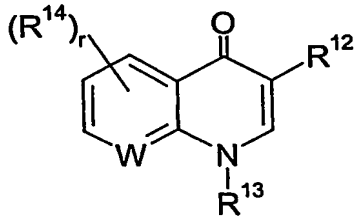
R^6 is hydroxy, or

R^5 and R^6 taken together with the intervening atoms form a cyclic group having the following structure:

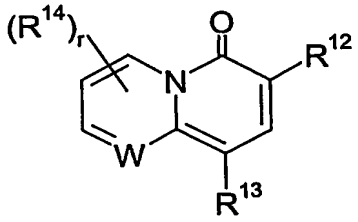


wherein Y is a bivalent radical selected from $-CH_2-$, -CH(CN)-, -O-, $-N(R^{11})-$ and $-CH(SR_8)-$;

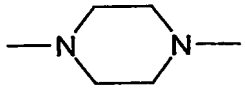
R^7 is a heterocyclic group having the following structure:



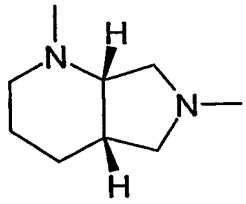
or



R^8 and R^9 are each independently selected from hydrogen and C_{1-4}alkyl;
R^{10} is hydrogen or NR^8R^9;
R^{11} is hydrogen or C_{1-4}alkyl substituted by a group selected from optionally substituted phenyl, optionally substituted 5 or 6 membered heteroaryl and optionally substituted 9 to 10 membered fused bicyclic heteroaryl;
R^{12} is hydrogen, $C(O)OR^{15}$, $C(O)NHR^{15}$ or $C(O)CH_2NO_2$;
R^{13} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, or optionally substituted phenyl or benzyl;
R^{14} is halogen, C_{1-4}alkyl, C_{1-4}thioalkyl, C_{1-4}alkoxy, NH_2, $NH(C_{1-4}alkyl)$ or $N(C_{1-4}alkyl)_2$;
R^{15} is hydrogen or C_{1-4}alkyl;
R^{16} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, optionally substituted phenyl or benzyl, acetyl or benzoyl;
X is $-U(CH_2)_sZ-$ or X is a group selected from:



and



U and Z independently are a divalent radical selected from $-N(R^{16})-$, -O-, $-S(O)_t-$, $-N(R^{16})C(O)-$, $-C(O)N(R^{16})-$ and $-N[C(O)R^{16}]-$;
W is a carbon or a nitrogen atom;
m is 0 or an integer from 1 to 5;
n, r and t are each independently selected from 0, 1 and 2;
p and q are each independently selected from 1 and 2; and
s is an integer from 2 to 8;

and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

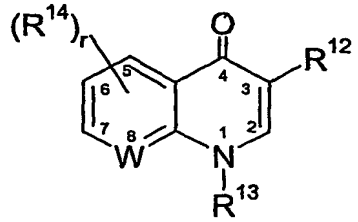
The compound of formula (I) and salts thereof may form solvates (e.g. hydrates) and the invention includes all such solvates.

In the general formula (I) as drawn the solid wedge shaped bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

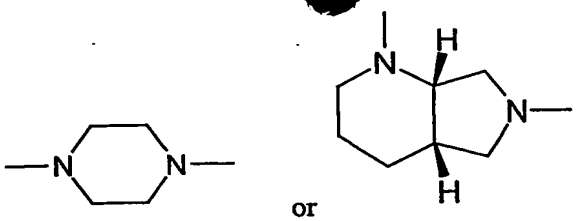
Compounds wherein R^2 represents a hydroxyl protecting group are in general intermediates for the preparation of other compounds of formula (I).

When the group OR^2 is a protected hydroxyl group this is conveniently an ether or an acyloxy group. Examples of particularly suitable ether groups include those in which R^2 is a trialkylsilyl (i.e. trimethylsilyl). When the group OR^2 represents an acyloxy group, then examples of suitable groups R^2 include acetyl or benzoyl.

When R^7 is a heterocyclic group having the following structure:

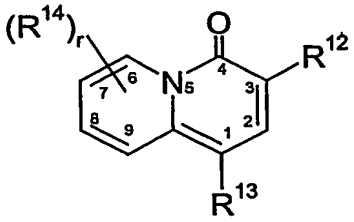


wherein W is carbon or nitrogen, said heterocyclic is linked in the 7 or 6 position to the Z group as above defined or to one of the nitrogen atoms contained in the following structures:

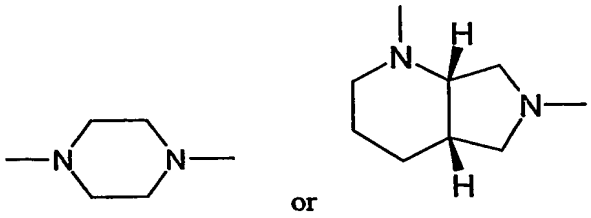


or

When R^7 is a heterocyclic group having the following structure:

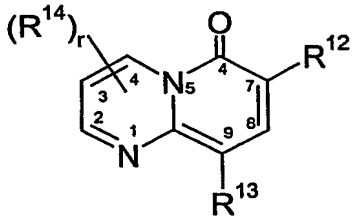


said heterocyclic is linked in the 8 or 7 position to the Z group as above defined or to one of the nitrogen atoms contained in the following structures:

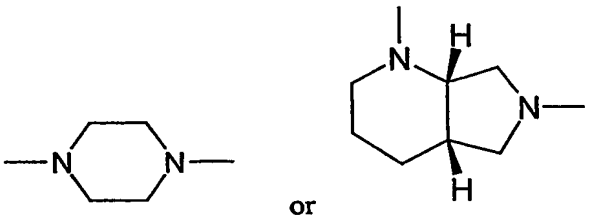


or

When R^7 is a heterocyclic group having the following structure:



said heterocyclic is linked in the 2 or 3 position to the Z group as above defined or to one of the nitrogen atoms contained in the following structures:



or

The term C_{1-4}alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl.

The term C_{2-6}alkenyl group as used herein as a group or a part of the group refers to a straight or branched alkenyl group containing from 2 to 6 carbon atoms; examples of such groups include 2-propenyl, 1-propenyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl and the like. It will be appreciated that in groups of the form -O-C_{2-6}alkenyl, the double bond is preferably not adjacent to the oxygen.

The term C_{3-7}cycloalkyl group means a non-aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term 5 or 6 membered heteroaryl as used herein as a group or a part of the group refers to furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridyl, pyridazinyl or pyrimidinyl.

The term 5 or 6 membered heterocyclic group as used herein as a group or part of the group refers to a monocyclic 5 or 6 membered saturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Examples of heterocyclyl groups include, but are not limited to, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholino, tetrahydropyranyl, tetrahydrofuranyl, and thiomorpholino.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term C_{1-4}alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or 2-methylprop-2-oxy.

The term 9 to 10 membered fused bicyclic heteroaryl as used herein as a group or a part of the group refers to quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzimidazolyl, benzothienyl, benzoxazolyl, 1,3-benzodioxazolyl, indolyl, benzothiazolyl, furylpyridine, oxazolopyridyl or benzothiophenyl.

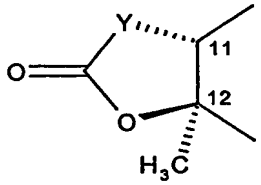
The terms optionally substituted phenyl, optionally substituted 5 or 6 membered heteroaryl, optionally substituted 9 to 10 membered fused bicyclic heteroaryl or optionally substituted 5 or 6 membered heterocyclic group refer to a group which is substituted by 1 to 3 groups selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxy, nitro, cyano, amino, C_{1-4}alkylamino or diC_{1-4} alkylamino, phenyl and 5 or 6 membered heteroaryl.

Preferred compounds of formula (I) are those wherein R^2 is hydrogen.

A representative example of R^3 is hydrogen.

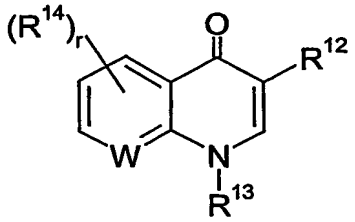
In one embodiment, R^4 is C_{1-4}alkyl optionally substituted by up to three substituents independently selected from optionally substituted 5 or 6 membered heteroaryl, OR^8, $S(O)_nR^8$, NR^8R^9, halogen and cyano. In another embodiment, R^4 is C_{1-4}alkyl optionally substituted by up to two substituents independently selected from optionally substituted 5 or 6 membered heteroaryl, OR^8, $S(O)_nR^8$, NR^8R^9, halogen and cyano. Representative examples of R^4 include C_{1-4}alkyl, for example methyl or isopropyl, optionally substituted by optionally substituted 5 or 6 membered heteroaryl such as pyridyl, OR^8 or $S(O)_nR^8$.

In one embodiment, R^5 is $O(CH_2)_pO(CH_2)_qR^{10}$, wherein R^{10} is preferably NR^8R^9. In another embodiment, R^6 is hydroxy. Alternatively, R^5 and R^6 taken together with the intervening atoms form a cyclic group having the following structure:



wherein Y is the bivalent radical -O-.

Representative examples of R^7 include heterocyclic groups having the following structure:



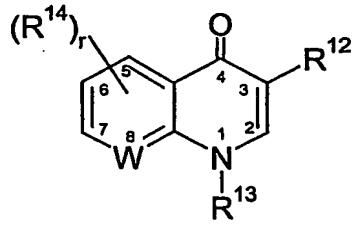
wherein W is preferably carbon.

Representative examples of R^8 and R^9 include C_{1-4}alkyl, for example methyl and ethyl.

A representative example of R^{12} is $C(O)OR^{15}$, wherein R^{15} is preferably hydrogen.

A representative example of R^{13} is C_{3-7}cycloalkyl, for example C_{3-6}cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, in particular cyclopropyl.

Representative examples of R^{14} include halogen, in particular fluorine and chlorine. When R^7 is a heterocyclic group having the following structure:



wherein W is preferably carbon, R^{14} is preferably fluorine or chlorine at the 6 or 7 position and the heterocyclic is linked in the unsubstituted 6 or 7 position to the X group.

A representative example of X is $-U(CH_2)_sZ-$. In particular, X is $-U(CH_2)_sZ-$ wherein U and Z are preferably –NH-.

Preferably m is 1 to 3, in particular 2.

A representative example of n is 0.

When p is 1, q is preferably 2.

A representative example of r is 1.

Preferably s is 2 to 4, in particular 2.

Particularly preferred compounds of the invention are:
4"-*O*-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11-*O*-(2-dimethylaminoethoxymethyl)-(9E)-methoximino erythromycin A,
4"-*O*-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-*O*-(2-propyl)oximino erythromycin A,
4"-*O*-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-methoximino erythromycin A, and
4"-*O*-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-*O*-(ethoxymethyl)oximino erythromycin A.

Compounds according to the invention also exhibit a broad spectrum of antibacterial activity against a wide range of clinical pathogenic microorganisms. Using a standard microtiter broth serial dilution test, compounds of the invention have been found to exhibit useful levels of activity against a wide range of pathogenic microorganisims. In particular, the compounds of the invention may be active against strains of Staphylococcus aureus, Streptopococcus pneumoniae, Moraxella catarrhalis, Streptococcus pyogenes, Haemophilus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae and Legionella pneumophila. The compounds of the invention may also be active against resistant strains, for example erythromycin resistant strains. In particular, the compounds of the invention may be active against erythromycin resistant strains of Streptococcus pneumoniae and Streptococcus pyogenes.

The compounds of the invention may therefore be used for treating a variety of diseases caused by pathogenic bacteria in human beings and animals.

Thus, according to another aspect of the present invention, we provide a compound of formula (I) or a physiologically acceptable salt thereof for use in the therapy or prophylaxis of systemic or topical bacterial infections in a human or animal subject.

According to a further aspect of the invention we provide the use of a compound of formula (I) or a physiologically acceptable salt thereof for the manufacture of a therapeutic agent for the treatment or prophylaxis of systemic or topical bacterial infections in a human or animal body.

According to a yet further aspect of the invention we provide a method of treatment of the human or non-human animal body to combat bacterial infections which method comprises administering to the body an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The compounds of the invention may be formulated for administration in any convenient way for use in human or veterinary medicine and the invention therefore includes within its scope pharmaceutical compositions comprising a compound of the invention adapted for use in human or veterinary medicine. Such compositions may be presented for use in conventional manner with the aid of one or more suitable carriers or excipients. The compositions of the invention include those in a form especially formulated for parenteral, oral, buccal, rectal, topical, implant, ophthalmic, nasal or genito-urinary use.

The compounds according to the invention may be formulated for use in human or veterinary medicine by injection (e.g. by intravenous bolus injection or infusion or via intramuscular, subcutaneous or intrathecal routes) and may be presented in unit dose form, in ampoules, or other unit-dose containers, or in multi-dose containers, if necessary with an added preservative. The compositions for injection may be in the form of suspensions, solutions, or emulsions, in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, solubilising and/or dispersing agents. Alternatively the active ingredient may be in sterile powder form for reconstitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The compounds of the invention may also be presented for human or veterinary use in a form suitable for oral or buccal administration, for example in the form of solutions, gels, syrups, mouth washes or suspensions, or a dry powder for constitution with water or other suitable vehicle before use, optionally with flavouring and colouring agents. Solid compositions such as tablets, capsules, lozenges, pastilles, pills, boluses, powder, pastes, granules, bullets or premix preparations may also be used. Solid and liquid compositions for oral use may be prepared according to methods well known in the art. Such compositions may also contain

one or more pharmaceutically acceptable carriers and excipients which may be in solid or liquid form.

The compounds of the invention may also be administered orally in veterinary medicine in the form of a liquid drench such as a solution, suspension or dispersion of the active ingredient together with a pharmaceutically acceptable carrier or excipient.

The compounds of the invention may also, for example, be formulated as suppositories e.g. containing conventional suppository bases for use in human or veterinary medicine or as pessaries e.g. containing conventional pessary bases.

The compounds according to the invention may be formulated for topical administration, for use in human and veterinary medicine, in the form of ointments, creams, gels, lotions, shampoos, powders, (including spray powders), pessaries, tampons, sprays, dips, aerosols, drops (e.g. eye ear or nose drops) or pour-ons.

Aerosol sprays are conveniently delivered from pressurised packs, with the use of a suitable propellant, eg dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas.

For topical administration by inhalation the compounds according to the invention may be delivered for use in human or veterinary medicine via a nebuliser.

The pharmaceutical compositions for topical administration may also contain other active ingredients such as corticosteroids or antifungals as appropriate.

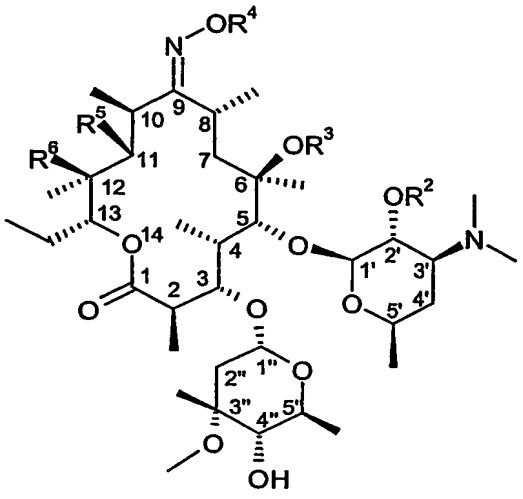
The compositions may contain from 0.01-99% of the active material. For topical administration, for example, the composition will generally contain from 0.01-10%, more preferably 0.01-1% of the active material.

For systemic administration the daily dose as employed for adult human treatment it will range from 2-100mg/kg body weight, preferably 5-60mg/kg body weight, which may be administered in 1 to 4 daily doses, for example, depending on the route of administration and the condition of the patient. When the composition comprises dosage units, each unit will preferably contain 200mg to 1g of active ingredient. The duration of treatment will be dictated by the rate of response rather than by arbitrary numbers of days.

Compounds of general formula (I) and salts thereof may be prepared by the general method outlined hereinafter. In the following description, the groups R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, X, Y, U, Z, W, m, n, p, q, r and s have the meaning defined for the compounds of formula (I) unless otherwise stated. The groups X^aR^{7a} and Z^aR^{7a} are XR^7 and ZR^7 as defined for formula (I) or groups convertible to XR^7 and ZR^7 respectively. Conversion of a group X^aR^{7a} or Z^aR^{7a} to a XR^7 or ZR^7 group typically arises if a protecting group is needed during the reactions described below. A comprehensive discussion of the ways in which such groups may be protected and methods for cleaving the

resulting protected derivatives is given in for example T.W. Greene and P.G.M Wuts in Protective Groups in Organic Synthesis 2nd ed., John Wiley & Son, Inc 1991.

Compounds of formula (I) wherein m is an integer 1 to 5, may be prepared by reaction of 4'' hydroxy of formula (II) with a suitable activated and protected derivative of the carboxylic acid (III), followed where necessary by subsequent removal of the hydroxyl protecting group R^2 and conversion of the X^aR^{7a} group to XR^7.



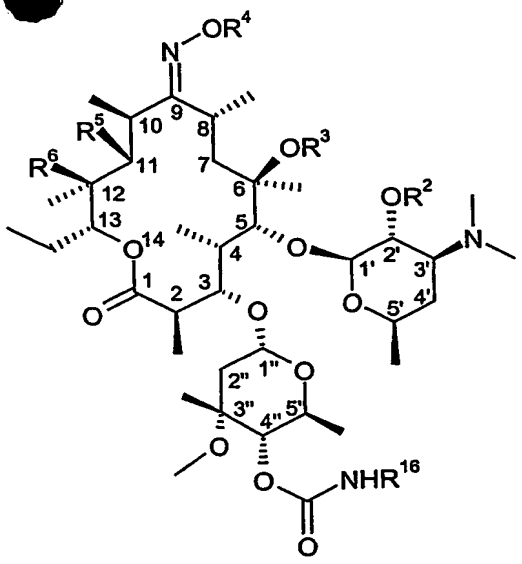
(II)

$HOC(O)(CH_2)_mX^aR^{7a}$
(III)

Suitable activated derivatives of the carboxyl group include the corresponding acyl halide, mixed anhydride or activated ester such as a thioester. The reaction is preferably carried out in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide optionally in the presence of a tertiary organic base such as dimethylaminopyridine or triethylamine or in the presence of inorganic base (i.e sodium hydride) and at a temperature within the range of 0° to 120°C.

Compounds of formula (I) wherein m is 0 and U is selected from $-N(R^{16})-$, -O- and $-S(O)_t-$ wherein t is 0, may be prepared by reaction of compounds of formula (II), in which the 4'' hydroxy is suitably activated, with a compound of formula X^aR^{7a} (IV), followed where necessary by subsequent removal of the hydroxyl protecting group R^2 and conversion of the X^aR^{7a} group to XR^7. Suitable activated derivatives of the 4'' hydroxy group include for example carbonyl imidazole. The reaction is preferably carried out in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide optionally in the presence of a tertiary base such as dimethylaminopyridine or triethylamine and at a temperature within the range of 0° to 120°C.

Compounds of formula (I) wherein m is 0 and U is $-N(R^{16})C(O)-$, may be prepared by reaction of compounds of formula (V),



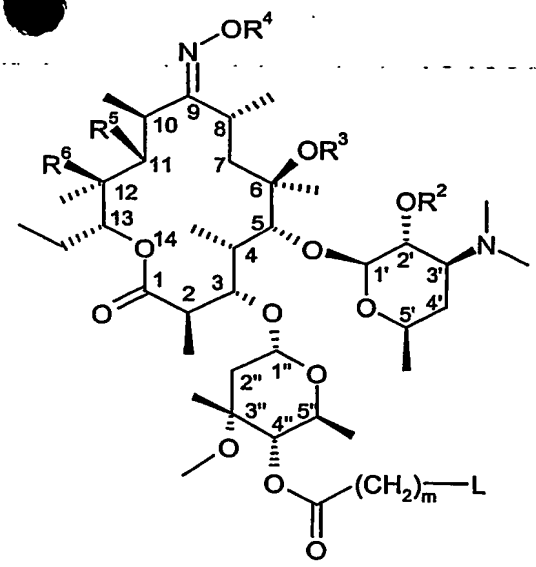
(V)

with a compound of formula $HOC(O)(CH_2)_sZ^aR^{7a}$ (VI), followed where necessary by subsequent removal of the hydroxyl protecting group R^2 and conversion of the Z^aR^{7a} group to ZR^7. The reaction is preferably carried out in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide optionally in the presence of a tertiary base such as dimethylaminopyridine or triethylamine and at a temperature within the range of 0° to 120°C.

Compounds of formula (V) may be prepared by treatment of compounds of formula (II), in which the 4" hydroxy is suitably activated, with an amine of formula NH_2R^{16} (VIIa). Suitable activated derivatives of the 4" hydroxy group include, for example, the carbonyl imidazole.

Compounds of formula (I) wherein m is 0 and U is $-C(O)N(R^{16})-$ may be prepared by reaction of 4'' hydroxy of formula (II) with a suitable activated derivative of the carboxylic acid $HOC(O)C(O)N(R^{16})(CH_2)_mZ^aR^{7a}$ (VIIb) followed where necessary by subsequent removal of the hydroxyl protecting group R^2 and conversion of the Z^aR^{7a} group to ZR^7.

In a further embodiment of the invention, compounds of formula (I) wherein m is 1 to 5 and U is a group selected from $-N(R^{16})-$, -O-, -S-, may be prepared by reaction of compounds of formula (VII),

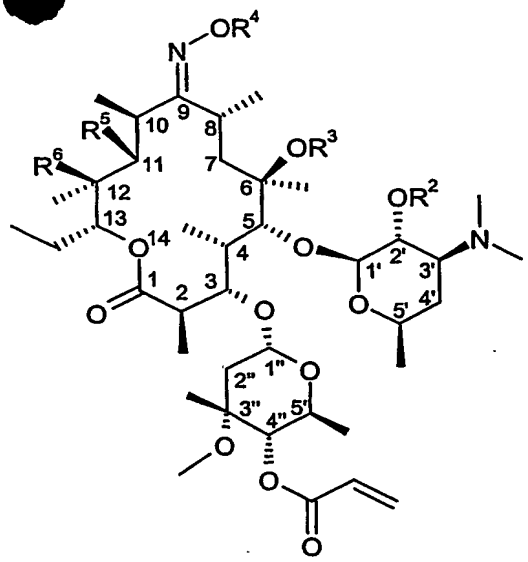


(VII)

wherein m is an integer from 1 to 5 and L is a suitable leaving group, with X^aR^{7a} (IV) in which U is a group selected from -N(R^{16})-, -O- and -S-. The reaction is preferably carried out in a solvent such as a halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran, dimethoxyethane), acetonitrile or ethyl acetate and the like), dimethylsulphoxide, N,N-dimethylformamide, 1-methyl-pyrrolidone and in the presence of a base, followed, if desired, by removal of the hydroxyl protecting group R^2 and conversion of the X^aR^{7a} group to XR^7. Examples of the bases which may be used include organic bases such as diisopropylethylamine, triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene, and inorganic bases such as potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxyde, sodium hydride, potassium hydride and the like. Suitable leaving groups for this reaction include halide (e.g. chloride, bromide or iodide) or a sulfonyloxy group (e.g. tosyloxy or methansulfonyloxy).

Compounds of formula (VII) may be prepared by reaction of a compound of formula (II), wherein R^2 is a hydroxyl protecting group, with a suitable activated derivative of the carboxylic acid $HOC(O)(CH_2)_mL$ (VIII), wherein L is a suitable leaving group as above defined. Suitable activated derivatives of the carboxyl group are those defined above for carboxylic acid (III). The reaction is carried out using the conditions described above for the reaction of a compound of formula (I) with carboxylic acid (III).

In a preferred embodiment of the invention, compounds of formula (I) wherein m is 2, U is a group selected from -N(R^{16})-, -O- and -S-, may be prepared by Michael reaction of a compound of formula (IX), wherein R^2 is a hydroxyl protecting group

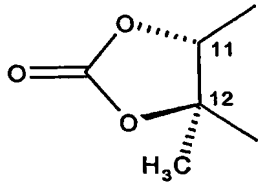


(IX)

with a compound of formula X^aR^{7a} (IV). The reaction is suitably carried out in a solvent such as dimethylsulphoxide, N,N-dimethylformamide, 1-methyl-pyrrolidone, a halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran, dimethoxyethane), acetonitrile or ethyl acetate or alcohol (e.g methanol, isopropanol) and the like, and in the presence of a base, followed, if desired, by removal of hydroxyl protecting group R^2 and conversion of the X^aR^{7a} group to XR^7.

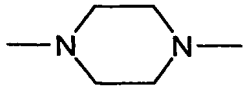
Compounds of formula (I) may be converted into other compounds of formula (I). Thus compounds of formula (I) wherein U is $-S(O)_t-$ and t is 1 or 2 may be prepared by oxidation of the corresponding compound of formula (I) wherein t is 0. The oxidation is preferably carried out using a peracid, e.g. peroxybenzoic acid, followed by treatment with a phosphine, such as triphenylphosphine. The reaction is suitably carried out in an organic solvent such as methylene chloride.

Compounds of formula (II), wherein R^5 or R^6 are hydroxy or R^5 and R^6 taken together with the intervening atoms form a cyclic group having the following structure:

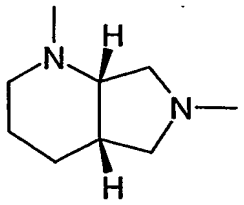


may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 284 203.

Compounds of formula (III) wherein X is $-U(CH_2)_sN(R^{16})-$, in which U is $-N(R^{16})-$, -O- or -S-, or X is a group selected from:

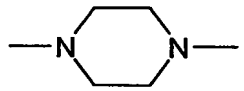


or



may be prepared by reaction of X^aR^{7a} (IV), wherein X^a has the meaning defined above with $R^{17}OC(O)(CH_2)_mL$ (X) wherein R^{17} is carboxyl protecting group and L is a suitable leaving group, followed by removal of R^{17}.

Compounds of formula (IV) wherein X is $-U(CH_2)_sZ-$ in which Z is $-N(R^{16})-$, -O- or -S-, or X is a group selected from:



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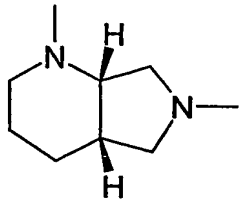


may be prepared by reaction of a compound of formula $R^{7a}L$ (XI), wherein L is a suitable leaving group such as chlorine, fluorine or bromine, with a compound of formula $-U(CH_2)_sZ-$ (XII) in which Z is $-N(R^{16})-$, -O- or -S-, with piperazine or with 1H-pyrrolo[3,4-b]pyridine, octahydro.

Suitable hydroxy protecting reagents are those described by T.W. Greene and P.G.M Wuts in Protective Groups in Organic Synthesis 2nd ed., John Wiley & Son, Inc 1991, which is incorporated by reference. Examples of suitable hydroxy protecting reagents include acetic anhydride, benzoic anhydride or a trialkylsilyl chloride in a protic solvent. Examples of aprotic solvents are dichloromethane, NN-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and the like.

Suitable R^{17} carboxyl protecting group include t-butyl, allyl or benzyl.

In order that the invention may be more fully understood the following examples are given by way of illustration only.

The following abbreviations are used in the text: DMSO for dimethyl sulfoxide and EtOH for ethanol.

Examples

Intermediate 1

2'-*O*-Acetyl-11-*O*-(2-dimethylaminoethoxymethyl)-(9E)-methoximino erythromycin A

A solution of 11-*O*-(2-dimethylaminoethoxymethyl)-(9E)-methoximino erythromycin A[1] (0.423 g, 0.5 mmol) in dichloromethane (40 mL) was treated with sodium hydrogen carbonate (0.126 g, 1.5 mmol) followed by acetic anhydride (0.056 g, 0.55 mmol). After stirring overnight at room temperature the mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL). The organic layer was separated, dried and evaporated to yield the title product as a solid. ESMS *m/z* 907 (100%) [MH^+].

Intermediate 2

2'-*O*-Acetyl-11,12-carbonate-(9E)-*O*-(2-propyl)oximino erythromycin A

The title compound was prepared from 11,12-carbonate-(9E)-*O*-(2-propyl)oximino erythromycin A[2] (0.6 g, 0.73 mmol) in similar fashion to that described for Intermediate 1. ESMS *m/z* 859 [MH^+].

Intermediate 3

2'-*O*-Acetyl-11,12-carbonate-(9E)-methoximino erythromycin A

The title compound was prepared from 11,12-carbonate-(9E)- methoximino erythromycin A[2] (0.615 g, 0.78 mmol) in similar fashion to that described for Intermediate 1. ESMS *m/z* 832 [MH^+].

Intermediate 4

2'-*O*-Acetyl-11,12-carbonate-(9E)-*O*-(2-pyridylmethyl)oximino erythromycin A

The title compound was prepared from 11,12-carbonate-(9E)-*O*-(2-pyridylmethyl)oximino erythromycin A[3] (0.095 g, 0.11 mmol) in similar fashion to that described for Intermediate 1. ESMS *m/z* 909 [MH^+].

Intermediate 5

2'-*O*-Acetyl-11,12-carbonate-(9E)-*O*-(methythiomethyl)oximino erythromycin A

The title compound was prepared from 11,12-carbonate-(9E)-*O*-(methylthiomethyl)oximino erythromycin A[3] (0.092 g, 0.11 mmol) in similar fashion to that described for Intermediate 1. ESMS *m/z* 878 [MH^+].

Intermediate 6

2'-*O*-Acetyl-11,12-carbonate-(9E)-*O*-(ethoxymethyl)oximino erythromycin A

The title compound was prepared from 11,12-carbonate-(9E)-*O*-(ethoxymethyl)oximino erythromycin A[2] (0.12 g, 0.14 mmol) in similar fashion to that described for Intermediate 1. ESMS *m/z* 876 [MH^+].

Intermediate 7

2'-*O*-Acetyl-11-*O*-(2-dimethylaminoethoxymethyl)-(9E)-methoximino-4''-*O*-propenoyl erythromycin A

To a solution of **Intermediate 1** (0.31 g, 0.34 mmol) in toluene (20 mL) was added triethylamine (0.069 g, 0.68 mmol) followed by 3-chloropropionyl chloride (0.052 g, 0.41 mmol) at room temperature. After stirring overnight the mixture was washed with water (10 mL), the organic layer separated, dried and evaporated to yield the title compound as a white solid. ESMS *m/z* 961 [MH^+].

Intermediate 8

2'-*O*-Acetyl-*O*-11,12-carbonate-(9E)-*O*-(2-propyloximino)-4''-*O*-propenoyl erythromycin A

The title compound was prepared from **Intermediate 2** (0.62 g, 0.72 mmol) in similar fashion to that described for **Intermediate 7**.

Intermediate 9

2'-*O*-Acetyl-11,12-carbonate-(9E)-methoximino-4''-*O*-propenoyl erythromycin A

The title compound was prepared from **Intermediate 3** (0.7 g, 0.84 mmol) in similar fashion to that described for **Intermediate 7**. ESMS *m/z* 886 [MH^+].

Intermediate 10

2'-*O*-Acetyl-11,12-carbonate-(9E)-*O*-(2-pyridylmethyloximino)-4''-*O*-propenoyl erythromycin A

The title compound was prepared from **Intermediate 4** (0.1 g, 0.11 mmol) in similar fashion to that described for **Intermediate 7**. ESMS *m/z* 963 [MH^+].

Intermediate 11

2'-*O*-Acetyl-11,12-carbonate-(9E)-*O*-(methythiomethyloximino)-4''-*O*-propenoyl erythromycin A

The title compound was prepared from **Intermediate 5** (0.096 g, 0.11 mmol) in similar fashion to that described for **Intermediate 7**. ESMS *m/z* 932 [MH^+].

Intermediate 12

2'-*O*-Acetyl-11,12-carbonate-(9E)-*O*-(ethoxymethyloximino)-4''-*O*-propenoyl erythromycin A

The title compound was prepared from **Intermediate 6** (0.12 g, 0.14 mmol) in similar fashion to that described for **Intermediate 7**.

Intermediate 13

6-[(2-Aminoethyl)amino]-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

7-Chloro-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (56.3 g) and ethylenediamine (36 g) were dissolved in N,N-dimethylacetamide (650 mL) at 100°C and stirred for 8.5 h at 115°C. Water (700 mL) was added to the reaction mixture cooled at room temperature. The reaction mixture was stirred at room temperature for 2 h, cooled at 0-5°C and stirred for 1 h. The precipitate obtained was filtered, washed with cold water, cold EtOH, and dried at 110°C under reduced pressure for 1 h. The crude product was treated with HCl (6% aqueous solution) heating for 1 h in the presence of charcoal. After filtration, the solution

was cooled to 35-40°C and a first precipitation happened. The precipitate was filtered, washed with water and dried at 110°C for 1 h. The title compound (6.4 g) was obtained as the hydrochloride salt. The hydrochloride salt was then converted to the free base using standard conditions.

Intermediate 14

4"-O-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-2'-O-acetyl-11-O-(2-dimethylaminoethoxymethyl)-(9E)- methoximino erythromycin A

A mixture of **Intermediate 7** (0.07 g, 0.07 mmol) and **Intermediate 13** (0.94 g, 0.29 mmol) in DMSO (5 mL), water (10 drops) and triethylamine (0.015 g, 0.15 mmol) was heated at 80°C. After 8 h the mixture was cooled and the crude mixture chromatographed over silica gel eluting with dichloromethane containing an increasing concentration of methanol/ammonium hydroxide to yield the title compound as a white solid. ESMS m/z 1282 [MH^+].

Intermediate 15

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-2'-*O*-acetyl-11,12-carbonate-(9E)-*O*-(2-propyl)oximino erythromycin A

The title compound was prepared by the method of **Intermediate 14** but using **Intermediate 8** (0.6 g, 0.065 mmol) and **Intermediate 13** (0.04 g, 0.13 mmol).

Intermediate 16

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-2'-*O*-acetyl-11,12-carbonate-(9E)-methoximino erythromycin A

The title compound was prepared by the method of **Intermediate 14** but using **Intermediate 9** (0.14 g, 0.16 mmol) and **Intermediate 13** (0.1 g, 0.31 mmol). ESMS m/z 1207 [MH^+].

Intermediate 17

4"-*O*-[3-[[2-[(3-Carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl) amino]ethyl]amino]propionyl]-2'-*O*-acetyl-11,12-carbonate-(9E)-methoximino erythromycin A

The title compound was prepared by the method of **Intermediate 14** but using **Intermediate 9** (0.07 g, 0.079 mmol) and 7-[(2-aminoethyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid[4] (0.048 g, 0.16 mmol).

Intermediate 18

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-2'-*O*-acetyl-11,12-carbonate-(9E)-*O*-(2-pyridylmethyl)oximino erythromycin A

The title compound was prepared by the method of **Intermediate 14** but using **Intermediate 10** (0.095 g, 0.11 mmol) and **Intermediate 13**. ESMS m/z 1282 [MH^-].

Intermediate 19

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-2'-*O*-acetyl-11,12-carbonate-(9E)-*O*-(methylthiomethyl)oximino erythromycin A

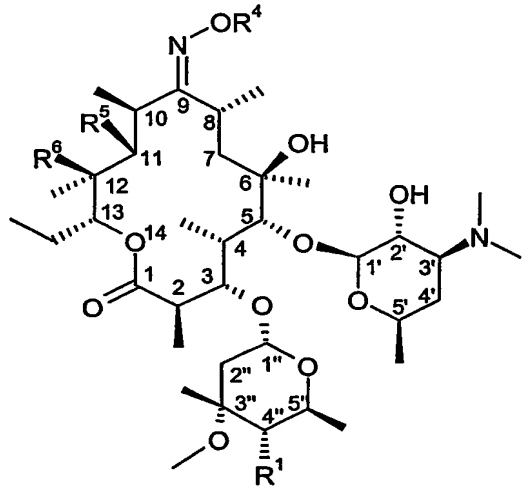
The title compound was prepared by the method of **Intermediate 14** but using **Intermediate 11** (0.095 g, 0.11 mmol) and **Intermediate 13**. ESMS m/z 1251 [MH^-].

Intermediate 20

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-2'-*O*-acetyl-11,12-carbonate-(9E)-*O*-(ethoxymethyl)oximino erythromycin A

The title compound was prepared by the method of **Intermediate 14** but using **Intermediate 12** (0.13 g, 0.14 mmol) and **Intermediate 13**. ESMS m/z 1249 [MH^-].

The compounds of **Examples 1 to 8** were prepared by the procedures described below.



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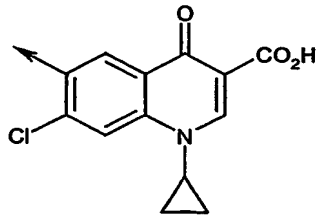

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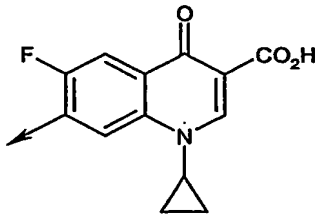


Example	R^1	R^4	R_5	R_6
1	$OC(O)(CH_2)_2N(H)(CH_2)_2NHA$	Me	$OCH_2O(CH_2)_2NMe_2$	OH
2	$OC(O)(CH_2)_2N(H)(CH_2)_2NHA$	*i*-Pr	R_5R_6 -O-C(O)-O-	
3	$OC(O)(CH_2)_2N(H)(CH_2)_2NHA$	Me	R_5R_6 -O-C(O)-O-	
4	$OC(O)(CH_2)_2N(H)(CH_2)_2NHB$	Me	R_5R_6 -O-C(O)-O-	
5	$OC(O)(CH_2)_2N(H)(CH_2)_2NHB$	*i*-Pr	R_5R_6 -O-C(O)-O-	
6	$OC(O)(CH_2)_2N(H)(CH_2)_2NHA$	2-pyridylCH_2	R_5R_6 -O-C(O)-O-	
7	$OC(O)(CH_2)_2N(H)(CH_2)_2NHA$	$MeSCH_2$	R_5R_6 -O-C(O)-O-	
8	$OC(O)(CH_2)_2N(H)(CH_2)_2NHA$	$EtOCH_2$	R_5R_6 -O-C(O)-O-	

Example 1

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11-*O*-(2-dimethylaminoethoxymethyl)-(9E)-methoximino erythromycin A

A solution of **Intermediate 14** (0.03 g, 0.023 mmol) in methanol (3 mL) was warmed at 50°C with stirring. After 16 h the mixture was cooled and the solvent evaporated to yield the title compound as a yellow solid. ESMS *m/z* 1240 [MH^+]. C^{13} NMR δ $CDCl_3$ 7.50, 9.20, 10.9, 13.6, 14.2, 17.4, 17.6, 18.2, 20.8, 21.2, 22.6, 23.9, 27.1, 31.2, 34.3, 34.6, 34.9, 35.7, 39.3, 39.9, 41.9, 43.0, 44.3, 44.7, 44.8, 47.5, 49.1, 58.8, 60.3, 63.5, 64.7, 66.8, 68.1, 71.5, 73.2, 74.4, 76.3, 77.6, 78.6, 78.8, 79.0, 84.4, 96.2, 98.9, 102.4, 104.1, 110.1, 118.9, 127.0, 127.4, 133.1, 143.4, 146.3, 167.4, 169.9, 172.5, 176.6, 177.2.

Example 2

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-*O*-(2-propyl)oximino erythromycin A

In an analogous procedure to that of **Compound 1**, **Intermediate 15** gave the title compound as a white solid. ESMS *m/z* 1192 [MH^+].

Example 3

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-methoximino erythromycin A

In an analogous procedure to that of **Compound 1**, **Intermediate 16** gave the title compound as a white solid. ESMS *m/z* 1165 [MH^+].

Example 4

4"-*O*-[3-[[2-[(3-Carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-methoximino erythromycin A

In analogous procedure to that of **Compound 1**, **Intermediate 17** gave the title compound as a white solid; ^1H NMR δ (CD_3OD) *inter alia* 8.78 (1H, s), 7.87(1H, d, J = 11.6 Hz), 7.35 (1H, d, J = 6.0 Hz).

Example 5

4"-*O*-[3-[[2-[(3-Carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-*O*-(2-propyl)oximino erythromycin A

A mixture of **Intermediate 8** (0.06 g, 0.066 mmol) and 7-[(2-aminoethyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid[4] (0.04 g, 0.13 mmol) in DMSO (3 mL) and diethylisopropylamine (0.029 mL, 0.17 mmol) was heated at 80°C for 8 h. After stirring at room temperature for 12 h the mixture was diluted with diethyl ether and the solid formed filtered to yield the title compound as a white solid. ESMS *m/z* 1176 [MH^+].

Example 6

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-*O*-(2-pyridylmethyl)oximino erythromycin A

In an analogous procedure to that of **Compound 1, Intermediate 18** gave the title compound as a white solid. ESMS *m/z* 1240 $[M-H]^-$.

Example 7

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-*O*-(methylthiomethyl)oximino erythromycin A

In an analogous procedure to that of **Compound 1, Intermediate 19** gave the title compound as a white solid. ESMS *m/z* 1210 $[M-H]^-$.

Example 8

4"-*O*-[3-[[2-[(3-Carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-*O*-(ethoxymethyl)oximino erythromycin A

In an analogous procedure to that that of **Compound 1, Intermediate 20** gave the title compound as a white solid. ESMS *m/z* 1207 $[M-H]^-$.

References

1. Knowles *et al., J. Antibiot.*, **1989**, *42*, 454-62.
2. Hunt *et al., J. Antibiot.*, **1989**, *42*, 1817-22.
3. EP 284203, **1988**.
4. Yoshida *et al J Pharm. Soc. Japan,* **1990**, *110*, 258.

Biological Data

The MIC (μg/ml) of test compounds against various organisms was determined including: *S. aureus* Smith ATCC 13709, *S. pneumoniae* SP030, *S. pyogenes* 3565, *E. faecalis* ATCC 29212, *H. influenzae* ATCC 49247, *M. catarrhalis* ATCC 23246.

Examples 1-3 and 6-8 have an MIC ≤ 1 μg/ml against *S. aureus* Smith ATCC 13709, *S. pneumoniae* SP030, *S. pyogenes* 3565 and *E. faecalis* ATCC 29212.

Examples 1 and 3 have an MIC ≤ 2 μg/ml against *H. influenzae* ATCC 49247 and *M. catarrhalis* ATCC 23246.

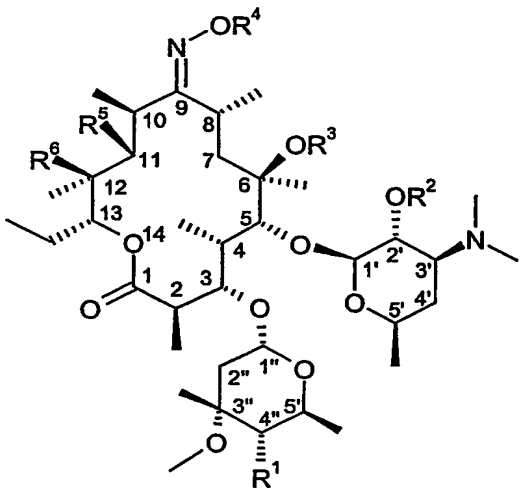
Examples 1-3 and 6-8 have an MIC <0.25 μg/ml against erythromycin resistant strains of *Streptococcus pneumoniae* and *Streptococcus pyogenes*.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take

the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A compound of formula (I)



(I)

wherein

R^1 is $OC(O)(CH_2)_mXR^7$;

R^2 is hydrogen or a hydroxyl protecting group;

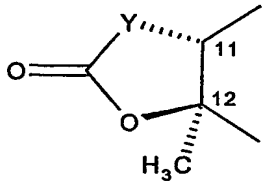
R^3 is hydrogen, C_{1-4}alkyl or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R^4 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl or a 5 or 6 membered heterocyclic group, wherein the alkyl, cycloalkyl, alkenyl and heterocyclic groups are optionally substituted by up to three substituents independently selected from optionally substituted 5 or 6 membered heterocyclic group, optionally substituted 5 or 6 membered heteroaryl, OR^8, $S(O)_nR^8$, NR^8R^9, $CONR^8R^9$, halogen and cyano;

R^5 is hydroxy, C_{3-6}alkenyloxy optionally substituted by 9 to 10 membered fused bicyclic heteroaryl or $O(CH_2)_pO(CH_2)_qR^{10}$,

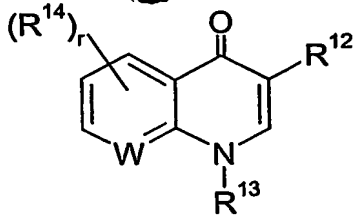
R^6 is hydroxy, or

R^5 and R^6 taken together with the intervening atoms form a cyclic group having the following structure:

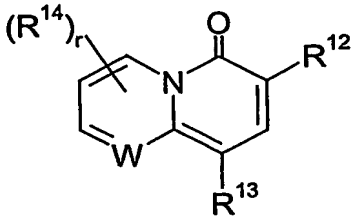


wherein Y is a bivalent radical selected from $-CH_2-$, -CH(CN)-, -O-, $-N(R^{11})-$ and $-CH(SR_8)-$;

R^7 is a heterocyclic group having the following structure:



or



R^8 and R^9 are each independently selected from hydrogen and C_{1-4}alkyl;

R^{10} is hydrogen or NR^8R^9;

R^{11} is hydrogen or C_{1-4}alkyl substituted by a group selected from optionally substituted phenyl, optionally substituted 5 or 6 membered heteroaryl and optionally substituted 9 to 10 membered fused bicyclic heteroaryl;

R^{12} is hydrogen, $C(O)OR^{15}$, $C(O)NHR^{15}$ or $C(O)CH_2NO_2$;

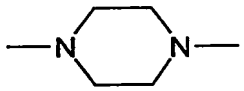
R^{13} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, or optionally substituted phenyl or benzyl;

R^{14} is halogen, C_{1-4}alkyl, C_{1-4}thioalkyl, C_{1-4}alkoxy, NH_2, $NH(C_{1-4}alkyl)$ or $N(C_{1-4}alkyl)_2$;

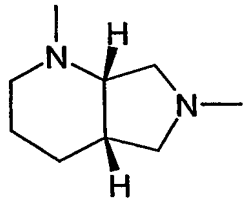
R^{15} is hydrogen or C_{1-4}alkyl;

R^{16} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, optionally substituted phenyl or benzyl, acetyl or benzoyl;

X is $-U(CH_2)_sZ-$ or X is a group selected from:



and



U and Z independently are a divalent radical selected from $-N(R^{16})-$, -O-, $-S(O)_t-$, $-N(R^{16})C(O)-$, $-C(O)N(R^{16})-$ and $-N[C(O)R^{16}]-$;

W is a carbon or a nitrogen atom;

m is 0 or an integer from 1 to 5;

n, r and t are each independently selected from 0, 1 and 2;

p and q are each independently selected from 1 and 2; and

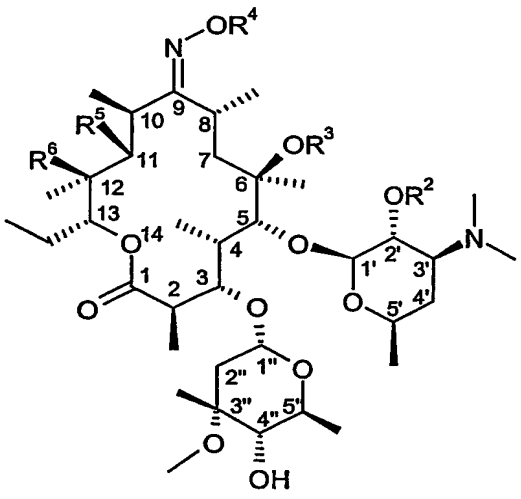
s is an integer from 2 to 8;

and pharmaceutically acceptable salts and solvates thereof.

2. A compound according to claim 1 as defined in any one of Examples 1 to 8, or a pharmaceutically acceptable salt or solvate thereof.

3. A compound selected from:
4"-*O*-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11-*O*-(2-dimethylaminoethoxymethyl)-(9E)-methoximino erythromycin A,
4"-*O*-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-*O*-(2-propyl)oximino erythromycin A,
4"-*O*-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-methoximino erythromycin A, and
4"-*O*-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-11,12-carbonate-(9E)-*O*-(ethoxymethyl)oximino erythromycin A.

4. A process for the preparation of a compound as claimed in claim 1 which comprises:
a) reacting a compound of formula (II)



(II)

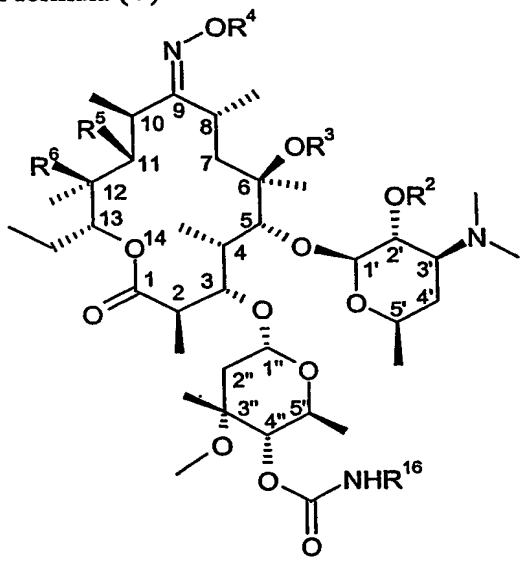
$HOC(O)(CH_2)_mX^aR^{7a}$
(III)

with a suitable activated derivative of the acid (III), wherein m is an integer 1 to 5, X^a and R^{7a} are X and R^7 as defined in claim 1 or groups convertible to X and R^7, to produce a compound of formula (I) wherein m is an integer 1 to 5;

b) reacting a compound of formula (II), in which the 4" hydroxy is suitably activated, with a compound of formula X^aR^{7a} (IV), wherein R^{7a} is R^{7a} as defined in claim 1 or a group convertible to R^7, s and Z have the meanings defined in claim 1 and X^a is $-U(CH_2)_sZ-$ or a group convertible to $-U(CH_2)_sZ-$, in which U is a group selected from selected from -

$N(R^{16})$- , -O-, and -S-, to produce a compound of formula (I) wherein m is 0 and U is a group selected from $-N(R^{16})-$, -O- and -S-;

c) reacting a compound of formula (V)

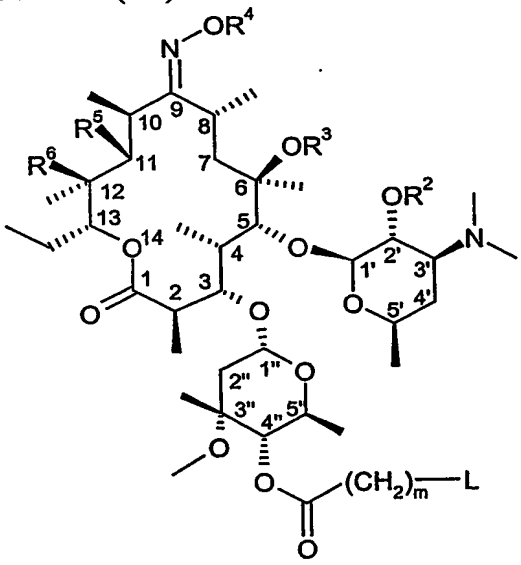


(V)

wherein R^{16} has the meaning defined in claim 1 with a suitable activated derivative of the carboxylic acid $HOC(O)(CH_2)_sZ^aR^{7a}$ (VI), wherein R^{7a} and Z^a are R^7 and Z as defined in claim 1 or groups convertible to R^7 and Z, to produce a compound of formula (I) wherein m is 0 and U is $-N(R^{16})C(O)-$;

d) reacting a compound of formula (II) with a suitably activated derivative of the carboxylic acid $HOC(O)C(O)N(R^{16})(CH_2)_sZ^aR^{7a}$ (VIIb) to produce a compound of formula (I) wherein m is 0 and U is $-C(O)N(R^{16})-$;

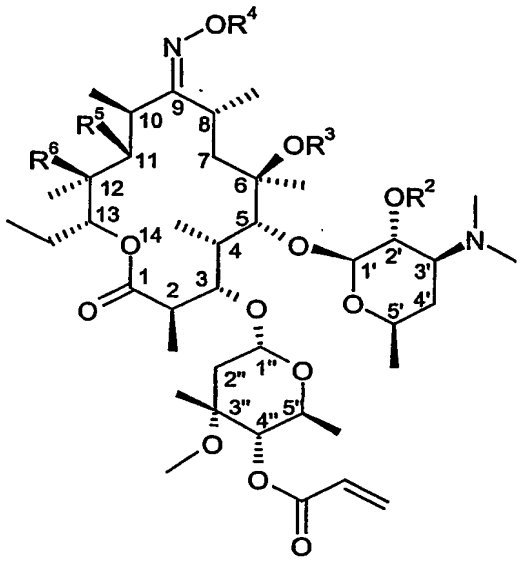
e) reacting a compound of formula (VII)



(VII)

with a compound of formula X^aR^{7a} (IV), wherein R^{7a} and X^a are R^7 and X as defined in claim 1 or groups convertible to R^7 and X, U is a group selected from -N(R^{16})-, -O- and -S-, and L is suitable leaving group, to produce a compound of formula (I) wherein m is 1 to 5 and U is a group selected from -N(R^{16})-, -O- and -S-; or

f) reacting a compound of formula (IX), with a compound of formula X^aR^{7a} (IV),



(IX)

wherein R^{7a} and X^a are R^7 and X as defined in claim 1 or groups convertible to R^7 and X, U is a group selected from -N(R^{16})-, -O- and -S-, to produce a compound of formula (I) wherein m is 2 and U is a group selected from -N(R^{16})-, -O- and -S-;

and thereafter, if required, subjecting the resulting compound to one or more of the following operations:
i) removal of the protecting group R^2,
ii) conversion of X^aR^{7a} or Z^aR^{7a} to XR^7 or ZR^7 respectively, and
iii) conversion of the resultant compound of formula (I) into a pharmaceutically acceptable salt or solvate thereof.

5. A compound as claimed in any one of claims 1 to 3 for use in therapy.

6. The use of a compound as claimed in any one of claims 1 to 3 in the preparation of a medicament for use in the therapy of systemic or topical bacterial infections in a human or animal body.

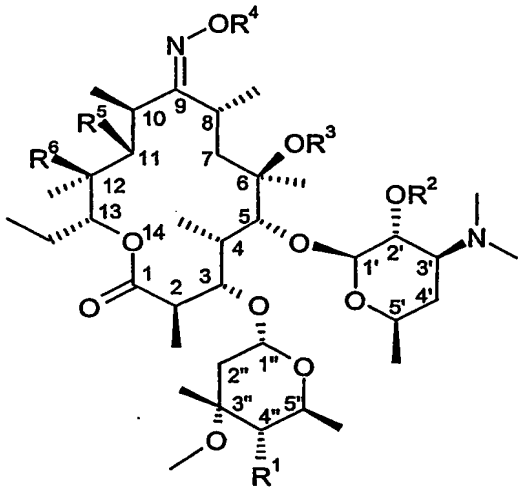
7. The use of a compound as claimed in any one of claims 1 to 3 for use in the treatment or prophylaxis of systemic or topical bacterial infections in a human or animal body.

8. A pharmaceutical composition comprising a compound as claimed any one of claims 1 to 3 in admixture with one or more pharmaceutically acceptable carriers or excipients.

9. A method for the treatment of the human or non-human animal body to combat bacterial infection comprising administration of an effective amount of a compound as claimed in any one of claims 1 to 3.

Abstract

The present invention relates to compounds of formula (I)



(I)

and pharmaceutically acceptable salts and solvates thereof, to processes for their preparation and their use in therapy or prophylaxis of systemic or topical bacterial infections in a human or animal body.

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